REMARKS

Claims 1-65 are pending in this application. Claims 1, 30, 40, 48 and 63 have been amended. Claims 64 and 65 have been added. The only difference between claim 64 and claim 1 and claim 65 and claim 40 is that probenecid is required in claims 64 and 65.

According to the Official Action claims 1-39, 42-45 and 48-63 are rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. This rejection is respectfully traversed.

Claim 1 has been amended to remove the phrase "under normal conditions of use".

Contrary to the examiner's statement, there is support for the phrase " the outer coating does not enhance the rate of drug release from the composition" in the original disclosure. As shown, *inter alia,* the use of the outer coating (Eudragit L30 D55) alone retards drug release and therefore it cannot be expected to enhance the drug release when used in combination with other polymers, which have also been shown to retard the drug release when used alone (See Table 1). This can also be inferred from page 3 of the specification ([0032] of the published application), which clearly indicates that the outer enteric polymeric coat controls the initial rapid release of the drug in acidic environment. Page 4 of the specification ([0061] of the published application) further provides support as it clearly mentions that the outer enteric polymer coating controls the initial rapid release of drug in the acidic environment and that the rate of drug release increases after the outer coating is dissolved and the inner coating is then used to control the release of the drug. A person of ordinary skill in the art would therefore infer that the outer coating is used to decrease the rate of drug release and not enhance it. Accordingly the limitation included in amended claim 1 filed in the last amendment is not new matter and is supported by the original specification. However, claim 1 has again been amended to indicate that the outer coating

controls the initial rapid release of the drug instead of indicating that the same does not enhance the rate of release of the drug.

The amendment of claim 1 to include "the outer coating controls the initial rapid release of cefuroxime axetil " from the composition is supported in the text on paragraph 4 corresponding to paragraph [0061] of the published application.

Claim 63 has been amended to correct an obvious typographical error. Therefore it is respectfully requested that this rejection be withdrawn.

The Examiner has rejected claims 1, 3-22 and 24-63 under 35 U.S.C. 103(a) as being unpatentable over US 4,897,270 to Deutsch et al ('270) in view of US 6,372,255 to Saslawski et al ('255) or '270 in view of US 5,578,316 to Bharadwaj et al ('255).

US 4,897,270 teaches a pharmaceutical tablet comprising a core containing cefuroxime axetil and a film coat. The present invention comprises coated granules, which, in an example of the invention may be compressed to form a tablet, which is not coated further.

'270 teaches that earlier film – coated tablets exhibit a gelling effect, which leads to poor disintegration of the tablet core and leads to poor dissolution and absorption of the drug (Column 1, lines 55-68). The invention of '270 is that it provides a film-coated tablet wherein the film coating ruptures very rapidly and the core then immediately disintegrates thus allowing dispersion and dissolution of the cefuroxime axetil in the gastrointestinal tract before any gelling effect can occur (Column 2, lines 3-11). Further, for the rapid rupture to take place, the film coat needs to be thin (Column 2, lines 63-66). The coatings suggested include Eudragit E and Eudragit E30D (Column 3, lines 35-37). The tablets incorporate disintegrants and other excipients in the core (Col 4) and plasticizers and other excipients in the coating (Col. 3). High and

low doses of cefuroxime axetil are taught in Examples 1 to 4 while amorphous material usage is suggested in Col 4, lines 66-67.

Since rapid disintegration is desired to increase dissolution, to a person of ordinary skill in the art, the teachings of '270 would suggest that for sustained release, the tablet should not disintegrate but should remain as a monolithic entity with the utilization of gel forming agents and/or the gelling effect of Cefuroxime axetil for sustained release. However, the present invention utilizes the rapid disintegration of an oral composition, an example of which is a tablet, to yield coated granules and achieves sustained release through these granules which is not obvious from the teachings of '270. As the Examiner rightly pointed out, Eudragit E and Eudragit E30D are polymers which are not used in the composition of claim 1 of this application. While the use of disintegrants to afford rapid disintegration for immediate release tablets is well known in prior art, here disintegrants are used to prepare a sustained release composition, which is novel. The disintegrants used herein overcome the limitation of gelling tendency of cefuroxime axetil and yet control its release by coating of the granules (see page 2 of the specification, Col. [0024]). The use of other excipients and plasticizers in the core and coatings respectively has been done to facilitate the current invention and thus cannot be claimed to be obvious from '270 wherein the aim of use of these excipients was entirely different i.e. to facilitate rapid rupture of the film and rapid disintegration. The higher limit of the doses of Cefuroxime axetil as claimed, for example, in claims 3 and 5 are not taught by '270 which is limited to the doses currently used in conventional tablets. Accordingly this teaches away from the present invention. The amorphous form has been claimed as one of the embodiments of this invention and reference for the same i.e. US 4,820,833 has been mentioned in the present specification (Page 1,Corresponding to paragraph [0008] of the published application).

US Patent 6,372,255 teaches a multilayer tablet for instant and prolonged release of active substances comprising an outer layer formed of an active agent and an excipient and an inner layer comprising a polymeric matrix in

which an active substance is dispersed, allowing the prolonged release of the active substance. Multilayer tablets of several drugs including cefuroxime axetil have been taught. Also, for prolonged release, copolymers derived from methacrylic acid and their derivatives, in particular ethylammonium methacrylate and methacrylate polymers and the polymers such as Eudragit RL 30 or RS 30 are suggested. Excipients for the tablets are proposed and so are disintegrants. A gastro resistant or entersoluble coating made of cellulose or copolymers of methacrylic acid such that the active agent is released only in the duodenal tract is also proposed.

The present invention envisages the use of bilayer tablets either for sustained release of cefuroxime axetil alone or in combination with probenecid either in controlled release form or for immediate release. The present invention requires the tablets to disintegrate in the body unlike the invention of '255 which requires a first layer to disintegrate and the second layer to remain intact throughout the release of the active ingredient (Col 2, lines 25-31). Thus, the second layer described in the '255 patent is similar to the teachings of US 4,897,270 which as discussed above, wherein the tablet is not allowed to disintegrate. However, '255 is silent as regards the use of the gelling effect which is expected in such intact Cefuroxime Axetil tablets and its result on the release profile. No release profile for Cefuroxime Axetil utilizing these polymers alone or in combination has been detailed in the patent.

Further, the polymers used for prolonged release in '255 are used as binders for making primary granules (Col 7,lines 9-10 and Col 9,lines 52-55). This is unlike the present invention wherein granules already prepared are further coated by granulation with the polymers in question (Page 6, col. [0086]) or by fluid bed coating (Page 6,col. [0087]).

While present invention does not make any distinction as regards the presence of disintegrating agents in the two layers, '255 specifically states that disintegrants should not be added to the prolonged release layer (Col 6, lines 56-59). Further, the use of enteric coatings in embodiments of this

invention is to control the release of the drug and not to facilitate the release of the drug in the duodenum as taught in '255. Accordingly the cited art does not teach the specific combinations of the polymers as found in the present invention and neither are they used to attain the end result as that of the present invention.

Accordingly this art cannot be regarded as rendering the present invention obvious.

US 5,578,316, teaches palatable compositions, which are granular in nature, and a method of masking the taste of unpleasant tasting drugs comprising the steps of coating the drug cores with separate layers of aqueous dispersions of methacrylate ester copolymers. Antibiotics are taught to be amongst the unpleasant tasting drugs and RS 30and RL 30 are used to mask the unpleasant taste and to provide an immediate release.

However, the invention of '316 relates mainly to chewable tablets and immediate release systems and not to sustained release systems (see for example Col 1,lines 12-13 and Col 2, lines 20-22).

Also, the polymers used herein are used for controlling release of Cefuroxime axetil and not for taste masking. Further, the invention of '316 mentions that Eudragit RL30D and RS 30D when applied as distinct coating layers produce an immediate release effect instead of the expected sustained release or enteric-coated effect. If one were to follow the teachings of '316 for Cefuroxime Axetil, one would not be able to obtain sustained release granules but would instead have immediate release granules. In fact, this patent teaches away from present invention as it discloses an immediate release of drug by use of these polymers and not sustained release of drug as claimed in this application. Thus, present invention is not obvious from '316.

Taken together, '270 teaches the use of film coating for preparing an immediate release, rapidly disintegrating tablet, '255 teaches the use of Eudragit RL and RS in a non-disintegrating system for controlled release as binders and '316 teaches the use of Eudragit RL and RS as a taste mask coating in immediate release granules. '270 and '316 are patents related to immediate release systems. On the other hand the present invention is a system, which rapidly disintegrates to yield granules coated using a ratio of, for example Eudragit L30 D 55, Eudragit RL 30 D and RS 30 D, which results in desired control over the release of Cefuroxime Axetil. Accordingly, the results obtained by the present invention in respect of control release of the drug Cefuroxime Axetil with the use of, for example, a ratio of Eudragit L30 D 55, Eudragit RL 30 D and RS 30 D is neither taught nor suggested from the teaching of the cited patents taken alone or in combination. The use of the inner coating and the outer coating as claimed in this application to obtain a fast disintegrating controlled release oral composition is unexpected and cannot be contemplated from the teachings of the cited art makes the present invention novel and inventive over the cited art.

Accordingly it is respectfully requested that the rejection be withdrawn.

As to the rejection of Claims 2 and 23 under 35 USC § 103(a) it is submitted that US 4,897,270, US 6,372,255, US 5,578,316 and further in view of US Patent 4,325,960 do not teach probenecid in cefuroxime axetil containing compositions.

US 4,325,960 suggests the use of probenicid for prolonging the effects of beta lactam antibiotics. It is however, silent as regards the quantity required for such prolongation as well as the duration of the prolongation. The present invention utilizes either the coated granule system alone or in combination with probenicid in an optimum quantity for sustained release of Cefuroxime Axetil, which is not obvious either from US 4,325,960 or all the cited art taken together.

Therefore it is respectfully requested that this rejection be withdrawn.

Applicants submit that the present application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted,

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